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In adults, glucose infusion results in a decreased glucose production rate (GPR) as a mechanism for maintaining euglycemia. To document the development of glucose homeostasis, we derived the GPR in 23 preterm appropriate for gestational age infants, 14 term appropriate for gestational age infants, and in 6 adults. After a 3-h fast, the average plasma glucose and insulin concentration was measured and the GPR was derived. During glucose infusion (5.6 +/- 0.3 mg X kg-1 min-1), compared with saline controls, the preterms had a rise in plasma glucose and plasma insulin, and the GPR was 1.4 mg X kg-1 min-1 (range, 0-4.4) vs. 3.0 mg X kg-1 min-1 (range, 1.8-4.1) (saline controls). In the term infants, only the plasma insulin concentration was elevated when the glucose infused (5.7 +/- 0.3 mg X kg-1 min-1) infants were compared with the saline controls and GPR was 0.4 X kg-1 min-1 (range, 0-2.6) vs. 3.4 mg X kg-1 min-1 (range, 2.8-5.7) (saline controls). In comparison to saline infused adults, glucose infusion (3.2 +/- 0.1 mg X kg-1 min-1) resulted in a significant rise in plasma glucose and in plasma insulin; and the GPR was reduced to 0.1 mg X kg-1 min-1 (range, 0-0.3) from 2.0 mg X kg-1 min-1 (range, 1.5-2.4). 5 of 13 preterms and 2 of 7 term infants had persistent […]

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Persistent Glucose Production during Glucose Infusion in the Neonate

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ABSTRACT In adults, glucose infusion results in a decreased glucose production rate (GPR) as a mechanism for maintaining euglycemia. To document the development of glucose homeostasis, we derived the GPR in 23 preterm appropriate for gestational age infants, 14 term appropriate for gestational age infants, and in 6 adults. After a 3-h fast, the average plasma glucose and insulin concentration was measured and the GPR was derived. During glucose infusion (5.6±0.3 mg·kg⁻¹·min⁻¹), compared with saline controls, the preterms had a rise in plasma glucose and plasma insulin, and the GPR was 1.4 mg·kg⁻¹·min⁻¹ (range, 0–4.4) vs. 3.0 mg·kg⁻¹·min⁻¹ (range, 1.8–4.1) (saline controls). In the term infants, only the plasma insulin concentration was elevated when the glucose infused (5.7±0.3 mg·kg⁻¹·min⁻¹) infants were compared with the saline controls and GPR was 0.4 mg·kg⁻¹·min⁻¹ (range, 0–2.6) vs. 3.4 mg·kg⁻¹·min⁻¹ (range, 2.8–5.7) (saline controls). In comparison to saline infused adults, glucose infusion (3.2±0.1 mg·kg⁻¹·min⁻¹) resulted in a significant rise in plasma glucose and in plasma insulin; and the GPR was reduced to 0.1 mg·kg⁻¹·min⁻¹ (range, 0–0.5) from 2.0 mg·kg⁻¹·min⁻¹ (range, 1.5–2.4). 5 of 13 preterms and 2 of 7 term infants had persistent GPR during glucose infusion; in contrast, the GPR in all adults was unmeasurable. There was no correlation between the plasma glucose concentration and the GPR in the newborn or in the adult. Both newborns and adults did have a correlation between plasma insulin concentration and the GPR; however, there was considerable variability in the neonate. We conclude that there are significant developmental differences in neonatal glucose homeostasis and that insulin is important in neonatal hormonal control of glucose production.

INTRODUCTION

The relationship between maternal and fetal plasma glucose concentrations, the repetitive occurrence of wide variations of neonatal glucose concentration, and the delayed disappearance of an acute glucose infusion in both the term and preterm infant indicate that regulation of neonatal carbohydrate metabolism is not well developed (1). The fetal plasma glucose concentration is regulated mainly by the maternal hormonal substrate balance, while birth brings the necessity of a period of adjustment to allow for independent neonatal regulation. In low birth-weight infants, this adjustment is delicate and may not be optimal resulting in abnormal consequences such as hypo- or hyperglycemia (2).

In contrast, fine control of the glucose production rate is characteristic of the adult response to glucose administration. Soskin et al. (3) originally proposed the hypothesis of autoregulation of hepatic glucose output by the magnitude of glucose delivery to the liver. By isotope dilution of radiolabeled glucose, Steele (4) showed that the mature sensitive response of hepatic control of glucose exists. When glucose is infused at a rate equal to hepatic glucose output, the rate of glucose production would be curtailed. Correspondingly, a new concentration of plasma glucose would plateau at a higher level when the glucose infusion rate was greater than the basal glucose production rate, depending on uptake under hormonal control.

Because radiolabeled tracers cannot be used in the pediatric age group, glucose kinetic studies using stable isotopes have been used to furnish quantitative data on the glucose production rate in newborns and infants.

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(5-8). To define the characteristics of neonatal glucose homeostasis, the glucose turnover rate was determined in prematurely born and full-term infants and compared to data obtained in the normal non-diabetic adult. In addition, the glucose production rate has been derived under conditions of glucose infusion. Documentation of the degree of suppression of the rate of glucose production can be used to characterize the control (or lack thereof) of neonatal glucose homeostasis in comparison to that of the adult.

METHODS

Subjects. The subjects included 37 infants and 6 normal adult women. All infants were appropriate for gestational age, defined as birth weight within the 10th and 90th percentile for gestation. 23 of the infants were preterm (<37 wk gestation) and 14 were term (≥37 wk gestation). The clinical characteristics of the infants' groups (birth weight, gestational age, and age at time of study) are noted in Table I. The infants were divided into two groups on the basis of whether they were preterm or term and subdivided on the basis of whether they received glucose or saline infusion during the study period. There were no significant differences in clinical characteristics within the preterm or term groups. As expected, the preterm group weighed significantly less and was born significantly earlier than the term group (P < 0.001). Both subgroups of preterm and term infants received similar concentrations of glucose during the study. There were no differences within or between groups in age at time of study. The APGAR scores at 1 and at 5 min were similar for all groups and all infants were well before and during the study.

The adult women were 31±2 yr of age and weighed 56.5±2.7 kg when they were studied under basal (saline) conditions. During a subsequent paired study at least 9 mo later, they received an infusate of 3.2±0.1 mg · kg⁻¹·min⁻¹ glucose. None of these women were pregnant or known to be diabetic at the time of the studies, or were taking oral contraceptives. Informed written consent was obtained from the adult subjects as well as from the mothers of the infants studied.

All infants were born at the Women and Infants Hospital of Rhode Island and all were cared for in the Special Care Nursery and were clinically stable and well during the study. All of the prematurely born infants required glucose administration intravenously to supplement limited oral intake. The term infants were being treated with glucose to administer antibiotics intravenously to treat a suspected infection (based on the clinical history perinatally). None of the infants were subsequently noted to have positive cultures or roentgen evidence of an infectious process. The clinical decision to administer glucose and antibiotics was made by the physicians responsible for the care of the infant. None were hypoglycemic clinically or by chemical determination. In 10 of the premature infants and 7 of the term infants the intravenous infusion was changed to 0.9% saline 1 h before beginning of the study. Dextrostatix determination of plasma glucose concentration was followed to assure that the infants were euglycemic.

Study design. During the study three base-line plasma samples were obtained before actual infusion of the d-U-¹³C tracer at 15-min intervals. The base-line samples included aliquots for evaluation of glucose, insulin, and natural glucose turnover rate percent ¹³C. Subsequently, the prime constant infusion technique was used to administer the tracer (9). A bolus equal to 50% of the d-U-¹³C glucose total dose was given intravenously for 1 min followed by the remaining 50% of the tracer in 0.9% saline at 4 µg in 0.06 ml · kg⁻¹·min⁻¹ for 110 min by IVAC pump model 630 (IVAC Corp., La Jolla, CA). The glucose infusion was calculated to deliver 6 mg glucose · kg⁻¹·min⁻¹. The glucose concentration of the infusate and the delivery rate were measured to determine the actual dose of glucose infused. After a 60-min equilibration period, plasma was obtained at four 15-min intervals to determine the glucose and insulin concentrations and the atom percent excess (APE). Plasma was also obtained for glucagon determination. The final period of 45 min of tracer infusion was the period from which the glucose turnover rate was determined and the glucose production rate was derived. Because the chemical determinations required 2 ml/kg of blood to be sampled, only one study (with either saline or glucose infusion) was performed on any one infant.

A similar protocol was used to study the adults. They were fasted for 10 h before the study and came to the hospital the morning of the evaluation. After a 30-min rest period, the base-line samples were obtained and then the infusion of saline or glucose was begun. 2 µg · kg⁻¹·min⁻¹ d-U-¹³C glucose was administered as the tracer.

Isotope tracer. d-U-¹³C glucose (78% enriched) (obtained from the National Stable Isotope Resource at the Los Alamos Scientific Laboratory) was used as the stable, non-radioactive tracer. The use of the isotope for human investigation had been approved by the Institutional Human Investigation Committees of Women and Infants Hospital and the Rhode Island Hospital, as well as Brown University. The lyophilized material from Los Alamos was prepared in a stock solution (500 µg/ml d-U-¹³C glucose in 0.45% NaCl) and tested for sterility and pyrogens (the latter by Ethide Sterilizing Corp., Coventry, RI) according to FDA standards. The solution was stored in sterile standard pharmacy containers in a refrigerator at 4°C.

Isolation and combustion of plasma glucose for ¹³C/¹²C analysis. The procedure for isolation and combustion of the plasma glucose is similar to the method reported by Wolfe et al. (10). Blood samples were centrifuged to separate the

| TABLE I  
<table>
<thead>
<tr>
<th>Clinical Characteristics of the Study Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Preterm</td>
</tr>
<tr>
<td>Glucose</td>
</tr>
<tr>
<td>Term</td>
</tr>
<tr>
<td>Glucose</td>
</tr>
</tbody>
</table>

* M±SEM.


2 Abbreviation used in this paper: APE, atom percent excess.
plasma. An internal standard of [U-14C]glucose (5,000 cpm in 30 μl) was added to a 200-μl aliquot of plasma before deproteinization with 1.8 ml 70% acetone. After centrifugation in a refrigerated Sorvall GCL-2 (Sorvall Manufacturing Co., Newtown, CT) for 10 min, the acetone in the supernate was removed on a Fisher Sample Concentrator 190 (Fisher Scientific, Medford, MA). The residual volume was pipetted on a Pasteur pipette exchange column composed of freshly prepared resins, 1.5 ml Dowex 1 (formate) (Bio-Rad Laboratories, Richmond, CA) layered over a 1.0-
ml Dowex 50 (hydrogen) (Bio-Rad Laboratories). The column was rinsed with fresh hot distilled water (CO2 free) to a total volume of 5 ml. An aliquot of 100 μl of the effluent was taken and counted for determination of the percent glucose recovered. An analysis of the specific percent recoveries shows that they varied over a relatively broad (53–95%) range so that the internal standard was critical to accurate determination of original glucose label recovered. There was a uniform recovery noted within each study (usually within 10%). The remaining effluent containing glucose and other neutral substances was collected and dried to ~100 μl, placed in a quartz sample tube, and combusted on a vacuum extraction line.

From each patient studied, an aliquot of blood was incubated overnight at room temperature. The erythrocytes metabolized the glucose and after 24 h a "zero plasma glucose blank" was obtained by centrifugation. This plasma blank allowed determination of the contribution of nonglucose sources to the total CO2 produced.

The 18/12CO2 produced by the combustion of each sample was isolated and measured in a 602D Isotopic Ratio Mass Spectrometer (Micromass, The Mass Spectrometry Co., Windsford, Cheshire, England) programmed to correct for gas mixing, background peaks, and 18O contribution to mass 45 according to the method of Craig (11) and referenced against a standard gas (12).

Calculations. Plasma glucose atom percent excess 13C was calculated from the 13/12C ion current ratio referenced to a gas sample of known isotopic content and corrected for recovery, for the zero plasma glucose blank and for the patient's natural plasma APE glucose 13C obtained from the base-line (preinfusion) samples.

Glucose turnover rate is equal to:

\[ \text{GTR (mg \cdot kg^{-1} \cdot min^{-1})} = \frac{\text{Isotope infusion rate/Plasma steady-state APE}}{\text{Glucose concentration (mg/dl)}} \]

where isotope infusion rate (micrograms d-[U-13C]glucose \cdot kilogram \cdot minute^{-1}) equals the infusate d-[U-13C]glucose concentration (micrograms/milliliters) \times infusate 13C APE infusion rate (milliliters \cdot kilogram \cdot minute^{-1}). The glucose concentration of the infusate was measured by hexokinase/glucose-6-phosphate dehydrogenase method (13). The APE of the infusate was 78 when saline was used as the diluent. When glucose was used as the diluent the specific APE of the infusate was determined. The glucose production rate for each infant and adult receiving a glucose infusion was the value obtained following subtraction of the glucose infusion rate from the total glucose turnover rate. When saline was infused, the glucose production rate equaled the glucose turnover rate.

Other methodology. Plasma glucose concentration was determined by the glucose oxidase method on a glucose analyzer (Yellow Springs Instrument Co., Yellow Springs, OH), insulin by a double antibody radioimmunoassay by a modification of the method of Hales and Randle (14), and glu-

cagon by a modification of the method of Falloona and Unger (15).

Unpaired t tests were used for statistical analyses in the neonatal studies and paired t tests in the adult studies. Multiple regression and discriminant analyses were used for correlation analyses.

RESULTS

Fig. 1 shows the mean plasma glucose concentrations during the study divided on the basis of whether the subjects received saline or glucose infusions. The data of the glucose concentration for each individual patient in each period (base line and turnover) were averaged if one specific value was unrecorded due to sampling difficulties. During the saline infusion turn-over period, the preterm infants' mean plasma glucose concentration (64±4 mg/dl) was comparable to that of the term infants' mean plasma glucose concentration (76±6 mg/dl) and significantly less than the value obtained for the adults (87±1 mg/dl) (P < 0.01). However, the term infants' mean plasma glucose concentration was not significantly different from the adults' mean plasma glucose concentration. During the glucose infused turnover period, the preterm infants' mean plasma glucose concentration (97±5 mg/dl) was not different from that noted for the term infants (93±8 mg/dl) or for the adults (114±7 mg/dl). However, the term infants' values were significantly lower than those of the adults (P < 0.05). There was a steady state of ±4% during the turnover period in all subjects for both saline and glucose infusion groups.

The average plasma glucose concentrations during the turnover period for all groups are shown in Table II. In preterm infants, the plasma glucose concentration was significantly elevated during glucose infusion in comparison to the saline controls (97±5 vs. 64±5 mg/dl) (P < 0.001). There was no significant rise in plasma glucose concentration in the term infants infused with glucose compared to saline infused controls (93±6 vs. 76±6 mg/dl) (P > 0.05). In the adults, glu-

![Figure 1](https://example.com/figure1.png)  
**Figure 1** Mean plasma glucose concentrations in newborns and adults with either saline or glucose infusion.
Table II
Metabolic Data during the Steady-State Turnover Period

<table>
<thead>
<tr>
<th>Group</th>
<th>Glucose infusion rate</th>
<th>n</th>
<th>Glucose (mg/dl)</th>
<th>Insulin (μU/ml)</th>
<th>Glucagon (μU/ml)</th>
<th>GPR* (μU/kg⁻¹ min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm</td>
<td>Saline</td>
<td>10</td>
<td>64±5</td>
<td>11±1</td>
<td>188±22</td>
<td>3.0 (1.8-4.1)</td>
</tr>
<tr>
<td></td>
<td>Glucose</td>
<td>13</td>
<td>97±5</td>
<td>19±3</td>
<td>228±35</td>
<td>1.4 (0.4-4.4)</td>
</tr>
<tr>
<td>Term</td>
<td>Saline</td>
<td>7</td>
<td>76±6</td>
<td>15±2</td>
<td>206±36</td>
<td>3.4 (2.8-5.7)</td>
</tr>
<tr>
<td></td>
<td>Glucose</td>
<td>7</td>
<td>93±6</td>
<td>26±5</td>
<td>183±32</td>
<td>0.4 (0-2.6)</td>
</tr>
<tr>
<td>Adult</td>
<td>Saline</td>
<td>6</td>
<td>87±1</td>
<td>14±1</td>
<td>199±39</td>
<td>2.0 (1.5-2.4)</td>
</tr>
<tr>
<td></td>
<td>Glucose</td>
<td>6</td>
<td>114±7</td>
<td>28±3**</td>
<td>153±35</td>
<td>0.1 (0-0.3)</td>
</tr>
</tbody>
</table>

Compared with saline control within the group.
* GPR, glucose production rate. ( ), range.
† M±SEM.
‡ P < 0.001.
§ P < 0.05.
¶ P < 0.02.
** P < 0.01.

Cose infusion resulted in a significant elevation of plasma glucose concentration compared to their saline control values (114±7 vs. 87±1 mg/dl) (P < 0.01).

Fig. 2 depicts the plasma insulin concentration during the study. During the turnover period the preterm infants' mean plasma insulin concentration was 11±1 μU/ml. This was not significantly different from the term infants' mean plasma insulin concentration (15±2 μU/ml) but was significantly lower than the mean plasma insulin concentration of the adults (19±3 μU/ml) (P < 0.05). During the glucose infused turnover period the preterm infants' mean plasma insulin concentration was similar to that of term infants (19±3 vs. 26±5 μU/ml, respectively), but was significantly lower than that obtained for the adults (19±3 vs. 28±3 μU/ml) (P < 0.05). As noted in Table II, all study groups had a significant rise in plasma insulin concentration during glucose infusion in comparison to saline controls (19±3 to 11±2 μU/ml vs. 26±5 to 15±2 μU/ml vs. 28±3 to 14±1 μU/ml for preterm, term, and adult groups, respectively).

Plasma glucagon concentration was also measured during the turnover period. The average values (as shown in Table II) during the saline infusion were 188±22 pg/ml for the preterm infants, 206±36 pg/ml for the term infants, and 199±39 pg/ml for the adults, which were not significantly different from each other.

Under conditions of glucose infusion, the preterm infants had a mean plasma glucagon value of 228±35 pg/ml; the term infants had a mean value of 183±32 pg/ml; and the adults had a mean plasma glucagon value of 153±35 pg/ml, which were also not significantly different from each other.

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Fig. 3 depicts the APE values (corrected for the preinfusate base-line APE) of the four samples obtained during the turnover period. There was a steady state noted for all groups irrespective of whether the subjects were infused with saline or glucose.

Fig. 4 illustrates the glucose production rate for each infant and adult studied during saline and/or glucose infusions. There was no significant difference in mean glucose turnover rate for the two newborn groups during saline infusion (3.0 and 3.4 mg·kg⁻¹min⁻¹ for the preterm and term infants, respectively) (Table II). The adults had a lower mean glucose turnover rate (2.0 mg·kg⁻¹min⁻¹) compared to both newborn groups (P < 0.001). When glucose was infused, 5 of 13 preterm infants and two of seven term infants had a glucose turnover rate >1.0 mg·kg⁻¹min⁻¹. In contrast, all adult subjects had a rate of glucose production <1.0 mg·kg⁻¹min⁻¹ in response to a glucose infusion.

Fig. 5 depicts the correlation between the peripheral plasma glucose concentration of the newborns and the adults during the turnover period related to the glucose production rate. Using discriminant analyses, the subjects were separated into two groups: one of all newborns and the other of the adults irrespective of whether they received saline or glucose. Using multiple regression analysis, there was obvious variability and no significant relationship between the two parameters in the newborn. The adults showed a bimodal distribution. Within each group there was no correlation between the peripheral plasma glucose concentration and the glucose production rate.

Fig. 6 depicts the correlation between the peripheral plasma insulin concentration during the turnover period and the glucose production rate. In the newborn considerable variability was noted in the glucose production rate when plasma insulin concentration was low. As the peripheral plasma insulin concentration rose, the glucose production rate fell so that for the group as a whole there was a significant correlation (P < 0.01). A similar but more consistent relationship with a higher degree of probability was noted in the adult (P < 0.001).

**DISCUSSION**

The purposes of the present investigation included: (a) documenting the degree of suppression of glucose production in response to a glucose infusion to characterize the control (or lack thereof) of glucose homeostasis in the neonatal period, and (b) evaluating the hormonal factors associated with the observed changes in neonatal glucose homeostasis.

The prime constant infusion technique of Steele was used with the stable nonradioactive isotope D-[U-¹³C]glucose in the human to determine the glucose turnover rate under steady-state plasma glucose conditions, and to derive the glucose production rate (9). However, we recognize that the use of D-[U-¹³C]glucose may not have been the optimal choice, since the total glucose production rate would generally be underestimated using this isotope in contrast to a less recycled glucose tracer. In studies of <2 h, recycling in normal term infants after 2 h of age resulted in a lower (3 to 20%) glucose turnover rate using [1-¹³C]glucose relative to the less recycled [6,6-²H]glucose (16). The use of D-
[U-13C]glucose includes nonrecycled as well as recycled carbon. Thus, the derived glucose turnover rate reported here is a "net" rate of glucose turnover. This may partially explain why our values with saline infusion are lower than those of Kalhan et al. (5) and Bier et al. (6).

The mechanism(s) involved in the reduction of the glucose production rate during glucose infusion can be related to: (a) a rise in beta cell activity with increased insulin production under glucose stimulation, and (b) the effect of glucose and insulin on the liver in modulating its rate of glucose production. In adults, numerous studies have clearly shown that both mechanisms are effectively operating to maintain normal plasma glucose concentration (10, 17-20). In the newborn, the apparent inefficiency of glucose homeostasis...
may be due to: (a) decreased insulin secretion in response to a glucose infusion, and (b) decreased hepatic or peripheral responsiveness to insulin or other hormones. Originally, an indirect technique of stepwise incremental glucose infusion was utilized in infants to infer the rate of basal glucose output compared to adults. The inference was predicated on the assumption that the newborn was as sensitive to minimal changes in glucose concentration as the adult (21). However, Varma et al. (22) initially showed that a 2-3-h infusion of glucose did not produce a steady state of plasma glucose concentration in the newborn dog as it did in the adult dog. They postulated that there was decreased hepatic and peripheral sensitivity to insulin.

This unresponsiveness to insulin was subsequently evaluated in the newborn lamb in which either saline or glucose was infused and the glucose production rate was derived using \([\text{6-}^3\text{H}]\text{glucose}\) (23). The glucose production rate persisted until the plasma insulin levels in the lamb were fivefold greater than that of the adult sheep. The data were interpreted to suggest that there was imprecise control of glucose production in the newborn lamb that may have been due to decreased hepatic sensitivity to insulin. These studies were extended to include infusion of insulin along with glucose. Although gluconeogenesis was suppressed when plasma insulin levels were in the 49-61\(\mu\text{U/ml}\) range, glucose production persisted until plasma insulin concentrations exceeded 200\(\mu\text{U/ml}\), irrespective of the plasma glucose concentration noted. Based on these data, we speculated that insulin might be the major hormone for control of glucose homeostasis (24).

In the current studies, the newborn infant, particularly in the preterm group, showed a persistent glucose production rate during glucose infusion. This persistence was probably not due to a decreased beta cell responsiveness to glucose since there was an increase in the average plasma insulin concentration after glucose infusion for both preterm and term infants during the turnover period (see Table II). However, it should be noted that there were a few infants in whom the plasma insulin concentration did not rise appreciably under glucose infusion (see Fig. 6). Plasma C peptide concentrations were not measured (and as such the actual concentration of insulin being secreted into the portal vein could not be determined). It is conceivable that in some instances there was not as brisk a beta cell response to the glucose infusion that would result in decreased insulin being delivered to the liver. A corresponding decreased peripheral plasma insulin concentration might be noted under these circumstances.

The other mechanism cited previously, i.e., decreased hepatic responsiveness to either glucose or insulin, could conceivably explain the persistence in glucose production rate in the glucose infused neonate. The lack of a relationship between our study infants' mean plasma glucose concentration and glucose production rate, which was shown previously by Hetenyi (25), suggests that glucose is not the major modulating stimulus for hepatic glucose production (Fig. 5). In the infants, there was a significant relationship between plasma insulin and the glucose production rate; however, in contrast to that seen in the adult, a marked variability in the relationship between plasma insulin and the glucose production rate was also observed (Fig. 6). These results are interpreted to suggest the presence of an inconsistent effect of insulin on the liver in the neonate (shown as marked variability) that may result in the apparent persistence of the rate of glucose production in the newborn. The reason for this blunted hepatic responsiveness to insulin is unclear but may be indicative of the transitional nature of control of glucose homeostasis during the neonatal period.

These data in the neonate are in marked contrast to that noted in the adults in our series and to that reported previously in the adult human and dog (17-20). For example, Madison has suggested that the control of plasma glucose following insulin administration is a direct effect of insulin on liver rather than a peripheral insulin effect on muscle (17, 18). Steele et al. showed a decrease by half of glucose delivery from the liver following 1-h infusion of 0.1\(\mu\text{U/kg per h}\) of insulin provided hypoglycemia was not present (19). These conclusions were recently reemphasized by Wolfe et al. who noted that intravenous glucose infusions at rates below that reported here resulted in suppression of glucose production (10). Finally, Rizza et al. suggested that half maximal suppression of glucose production occurred at insulin levels of 29±2\(\mu\text{U/ml}\) and that glucose production is more sensitive to changes in plasma insulin concentration than is utilization (20).

There were no significant differences in plasma glucagon concentration in any of the newborn or adult groups under conditions of saline or glucose infusion. The data are interpreted to suggest that glucagon is of lesser importance than insulin in the control of glucose production under conditions of glucose infusion, as might be expected.

The clinical significance of our data relate to the mechanism of hyperglycemia in the preterm low birth weight infant. Previous reports have firmly established the higher risk of hyperglycemia in the preterm low birth weight infant weighing <1,500 g (26-28). The mechanism of this clinical problem may be explained at least partially by the developmental difference in
glucose control reported here. In the neonate, particularly the preterm neonate, under conditions of glucose infusion, there was variability and lack of suppression of the rate of glucose production, which would partially account for the elevation of plasma glucose concentration at a new steady state. In contrast, under similar conditions, the adult completely suppressed the rate of glucose production. It is recognized that in both the newborn and the adult subjects the rate of glucose infusion exceeded the calculated glucose turnover rate during saline infusion. This might also contribute to the elevation of plasma glucose concentration noted, but would not explain the variable suppression of the rate of glucose production.

In summary, glucose production rates were derived in the premature and term infant with saline or glucose infusions to define neonatal glucose control and were contrasted with results obtained in the adult. The preterm and term infants had a variably persistent glucose production rate, whereas all adults had a suppressed rate of glucose production in response to a glucose infusion. While the glucose production rate was not related to neonatal plasma glucose concentration, it was related to neonatal plasma insulin concentration but to a lesser degree than in the adult. Insulin appears to be important in the hormonal control of neonatal glucose production.

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REFERENCES


